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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/692,537	10/24/2003	Lan Kluwe	NNFF-1 CON	9877

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EXAMINER	
KIM, YOUNG J	
ART UNIT	**PAPER NUMBER**
1637	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/692,537	KLUWE, LAN	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-4,8-10,14 and 19* is/are pending in the application.

4a) Of the above claim(s) *4* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,8-10,14 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The present Office Action is responsive to the Amendment received on January 22, 2007.

Election/Restrictions

This application contains claim 4 drawn to an invention nonelected with traverse in the Election received on June 5, 2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Preliminary Remark

Claims 1, 5-7, 11-13, and 15-18 are canceled.

Claims 2, 3, 8-10, 14, and 19 are under prosecution herein.

Claim Objections

The objection to claims 8-10 and 14 for being dependent on a non-elected invention (claim 4), made in the Office Action mailed on August 15, 2006 is withdrawn in view of the Amendment received on January 22, 2007.

Claim Rejections - 35 USC § 112

Claims 5, 8, and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, made in the Office Action mailed on August 15, 2006 is withdrawn in view of the Amendment received on January 22, 2007. Specifically, the rejection of claims 5 and 18 are withdrawn in view of their cancellation. The rejection with respect to claim 8 is withdrawn in view of the claim amendment.

Rejection, New – Necessitated by Amendment

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 recites the limitation, "the polymorphous DNA microsatellite marker has a length of up to approximately 300 bp."

The parent claim 19 recites that the method employs "one or more" microsatellite markers. Hence, it becomes indefinite which of the one or **more** markers, "the polymorphous DNA microsatellite marker" is being referred to.

Amending the claim to recite, "said one or more polymorphous DNA microsatellite markers," would overcome this rejection.

Claim Rejections - 35 USC § 103

The rejection of claim 5 rejected under 35 U.S.C. 103(a) as being unpatentable over Allione et al. (International Journal of Cancer, 1998, vol. 75, pages 181-186) in view of Cohen et al. (U.S. Patent No. 5,945,522, issued August 31, 1999) and Skolnick et al. (U.S. Patent No. 5,624,819, issued April 29, 1997), made in the Office Action mailed on August 15, 2006 is withdrawn in view of the Amendment received on January 22, 2007, canceling the rejected claim.

The rejection of claims 2, 3, 8-10, 14, and 19 under 35 U.S.C. 103(a) as being unpatentable over Cohen et al. (U.S. Patent No. 5,945,522, issued August 31, 1999) in view of Skolnick et al. (U.S. Patent No. 5,624,819, issued April 29, 1997) and Jacoby et al. (American Journal of Human Genetics, 1997, vol. 61, pages 1293-1302), made in the Office Action mailed on August 15, 2006 is withdrawn in view of the Amendment received on January 22, 2007.

With regard to the rejection of claims 5 and 18, over the same references of record, the rejection is withdrawn, based their cancellation.

Rejections, Maintained

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 2, 3, 8, 9, 14, and 19 under 35 U.S.C. 103(a) as being unpatentable over Allione et al. (International Journal of Cancer, 1998, vol. 75, pages 181-186) in view of Cohen et al. (U.S. Patent No. 5,945,522, issued August 31, 1999) and Skolnick et al. (U.S. Patent No. 5,624,819, issued April 29, 1997).

In addition, **claim 10** is included herein as being necessitated by Amendment.[1]

Applicants' arguments presented in the Amendment received on January 22, 2007 have been fully considered but they are not found persuasive for the reasons set forth in the, "Response to Arguments," section.

The Rejection:

Allione et al. disclose a method of determining the loss of heterozygosity in a patient suffering from tumor, wherein the method comprises the steps of:

a) amplifying one of more microsatellite polymorphic markers from a patient samples, wherein the samples are both blood and tumor tissue (page 181, 2nd column, *Tumor Samples* and *Genetic-marker analysis*), wherein the mircrosatellite markers are for tumor suppressor gene disease

(breast cancer; page 185, 1st column, 1st paragraph; page 185, 2nd column, 2nd paragraph, see the discussion regarding TSG (thus a tumor suppressor genes);

b) comparing the amount and length of the amplified polymorphous DNA microsatellite markers from blood and tumor sample (breast carcinomas; page 185, 1st column, 1st paragraph; see Figure 1);

c) establishing that the loss of an allele in the tumor of the patient based on this comparison (Figure 1).

Allione et al. are not explicit in discussing that the method also further comprise testing of an offspring of the individual, wherein the testing comprises the steps of amplifying for the same microsatellite markers from the blood of the offspring, wherein if the offspring inherits the allele that was retained in the tumor of the patient, determining that the offspring has an increased risk of developing the tumor suppressor gene disease (i.e., breast cancer).

Cohen et al. describe a way in which LOH is often employed for deriving at a possible tumor marker:

> "One mapping technique, called the loss of heterozygosity (LOH) technique, is often employed to detect genes in which a loss of function results in a cancer, such as the tumor suppressor genes described above. Tumor suppressor genes often produces cancer via two hit mechanism in which a first mutation, such as a point mutation (or a small deletion or insertion) inactivates one allele of the tumor suppressor gene. Often, ***this first mutation is inherited*** from generation to generation." (column 2, lines 57-65).
>
> The artisans continue:

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[1] Applicants have amended claim 10 from a specific marker of neurofibromatosis gene to a generic tumor suppressor gene disease marker, which is clearly taught by Allione et al. Hence, this amendment renders claim 10 rejectable over the prior art of record, the rejection of which is clearly necessitated by Amendment.

> "As a consequence of the deletion in the tumor suppressor gene, one allele is lost for any genetic marker located close to the tumor suppressor gene. Thus, if the patient is heterozygous for a marker, the tumor tissue loses heterozygosity, becoming homozygous or hemizygous. This loss of heterozygosity generally provides strong evidence for the existence of a tumor suppressor gene in the lost region. By genotyping pairs of blood and tumor samples from affected individuals with a set of highly polymorphic genetic markers, such as microsatellites, covering the whole genome, one can discover candidate locations for tumor suppressor genes." (column 3, lines 4-15).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to employ the teachings of Allione et al. and Cohen et al. for method of determining the risk of an offspring of the patient for the same cancer, thereby arriving at the claimed invention for the following reasons.

As already discussed by Cohen et al., it is well known in the art of cancer diagnostics that a cell comprising at least one normal copy of the tumor suppressor gene (i.e., heterozygote) will not give rise to a tumor.

Cohen et al. clearly convey the knowledge of the art, wherein mutation present in parent is inherited in the offspring from generation to generation. Thus, one of ordinary skill in the art at the time the invention was made would have been motivated to assay for the identified microsatellite markers in the offspring, so as to assess the risk of said offspring for the same cancer by determining whether the offspring inherited the same allele which was found to be present in the tumor of the parent patient.

Such concept was clearly present in the art at the time the invention was made as Skolnick et al. demonstrate:

> "One of the hallmarks of several tumor suppressor genes characterized to date is that they are deleted at high frequency in certain tumor types. The deletions often involve loss of a single allele, so-called loss of heterozygosity (LOH), but may also involve homozygous deletion of both alleles. For LOH, the ***remaining allele is presumed to be nonfunctional, either because of pre-existing inherited mutation***, or because of secondary sporadic mutation (column 2, lines 19-24).

Clearly based on such knowledge, one of ordinary skill in the art would have been naturally led to screen for the remaining "nonfunctional" tumor suppressor genes in the offspring of in individual who is afflicted with tumor suppressor gene disease (e.g., cancer), so as to assess the offspring's degree of risk for developing the same disease, rendering claims 19, 2, 10, and 14 obvious.

With regard to claims 3, 5, 8, and 9 the polymorphic microsatellite markers which show LOH in the method of Allione et al. are at least 4 markers in total (Figure 1).

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Response to Arguments:

Applicants traverse this rejection.

Applicants state that in the present method, "the presence in the offspring of the allele that is **retained** in the tumor of the afflicted individual indicates an increased risk of developing the tumor suppressor gene disease." (page 10, 2nd paragraph, Response)

Applicants contend that Allione et al. refer to the determination of the loss of heterozygosity in patients with breast carcinomas, but are silent about the importance of the determination of which allele is retained in the tumor. Applicants state that Allione et al. merely refers to detecting the loss of heterozygosity and that loss of heterozygosity is insufficient to determine whether an

offspring of an afflicted individual is at risk for developing diseases (page 11, 1st paragraph, Response).

This argument is not found persuasive.

What Allione et al. disclose is the determination of the allele that is lost in the tumor sample, by comparing the same set of microsatellite markers from the tumor sample and the blood sample from a patient.

The artisans clearly disclose that LOH was discovered in the tumor sample (a loss of an allele).

To reiterate, Allione et al. disclose a method of determining the loss of heterozygosity in a patient suffering from tumor, wherein the method comprises the steps of:

a) amplifying one of more microsatellite polymorphic markers from a patient samples, wherein the samples are both blood and tumor tissue (page 181, 2nd column, *Tumor Samples* and *Genetic-marker analysis*), wherein the mircrosatellite markers are for tumor suppressor gene disease (breast cancer; page 185, 1st column, 1st paragraph; page 185, 2nd column, 2nd paragraph; see the discussion regarding TSG (thus a tumor suppressor genes);

b) comparing the amount and length of the amplified polymorphous DNA microsatellite markers from blood and tumor sample (breast carcinomas; page 185, 1st column, 1st paragraph; see Figure 1);

c) establishing that the loss of **an allele in the tumor** of the patient based on this comparison (Figure 1).

In addition, one of ordinary skill in the art at the time the invention was made would have clearly recognized that the allele that is lost in the tumor is correlated with tumor.

This knowledge has been clearly demonstrated by the supporting artisans, for example, by Cohen et al.:

> "Tumor suppressor genes often produces cancer via two hit mechanism in which a first mutation, such as a point mutation (or a small deletion or insertion) **inactivates one allele of the tumor suppressor gene**. Often, ***this first mutation is inherited*** from generation to generation." (column 2, lines 57-65).

The artisans continue:

> "As a **consequence of the deletion in the tumor suppressor gene, one allele is lost for any genetic marker located close to the tumor suppressor gene**. Thus, if the patient is heterozygous for a marker, the tumor tissue loses heterozygosity, becoming homozygous or hemizygous. **This loss** of heterozygosity generally **provides strong evidence for the existence of a tumor suppressor gene in the lost region**. **By genotyping pairs of blood and tumor samples from affected individuals with a set of highly polymorphic genetic markers, such as microsatellites, covering the whole genome, one can discover candidate locations for tumor suppressor genes**." (column 3, lines 4-15).

Clearly, one of ordinary skill in the art would have recognized that the lost allele (LOH) in the tumor suppressor gene would have produced a strong evidence of correlation to tumor.

Such knowledge is again evidenced by Skolnick et al. demonstrate:

> "One of the hallmarks of several tumor suppressor genes characterized to date is that they are deleted at high frequency in certain tumor types. The deletions often involve loss of a single allele, so-called loss of heterozygosity (LOH), but may also involve homozygous deletion of both alleles. For LOH, the ***remaining allele is presumed to be nonfunctional, either because of pre-existing inherited mutation***, or because of secondary sporadic mutation (column 2, lines 19-24).

Hence, one of ordinary skill in the art would have been clearly motivated to assay for the microsatellite polymorphic region for determination of the allele that is lost in the tumor, so as to determine whether or not **the allele that was lost in the tumor of the parent** was **also lost in the offspring,** the loss of which would clearly implicate that said offspring is at an increased risk for cancer.

This is consistent with Applicants' own disclosure of their invention on page 11 of the instant specification, wherein Applicants assay a microsatellite polymorphic region, identifying two alleles (2 and 3) from the blood of the afflicted individual, followed by the assay for the same microsatellite polymorphic region, discovering that allele 3 had been lost in the tumor sample.

Applicants then assay for the same microsatellite polymorphic region from the blood of an offspring, wherein Applicants discover that the allele which was lost in the tumor of the parent was not lost in the offspring, concluding that, "it can thus be concluded that the allele which is **probably exclusively responsible for the disease was not inherited by the descendent**." (page 11, 1st paragraph, instant specification).

This is analogous to saying that if the allele that was lost in the parent was also lost in the offspring, then the offspring is at an increased risk for cancer.

Clearly, Applicants are assaying whether or not the allele that is lost in the tumor is also lost in the offspring, the knowledge of which was clearly available to one of ordinary skill in the art at the time the invention was made as evidenced by Cohen et al. and Skolnick et al.

The rejection is thus proper and thus maintained.

Double Patenting

The rejection of claims 5 and 18 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 of U.S. Patent No. 6,660,477 (herein, '477 patent), made in the Office Action mailed on August 15, 2006 is withdrawn in view of the Amendment received on January 22, 2007, canceling the rejected claims.

Rejection, Maintained

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible

harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The rejection of claims 2, 3, 8-10, 14, and 19 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 of U.S. Patent No. 6,660,477 (herein, '477 patent), made in the Office Action mailed on August 15, 2006 is maintained for the reasons already of record.

Applicants state a terminal disclaimer will be filed upon indication of allowable subject matter in the application (page 14, Response).

As there is no terminal disclaimer filed as of the date of the instant office communication, the rejection is maintained for the reasons of record.

The Rejection:

Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Claims 1-16 of '477 patent are drawn to a method of determining whether an offspring of an individual afflicted with neurofibromatosis, wherein the method comprises the steps of amplifying polymorphic microsatellite markers from tumor and blood samples from the individual afflicted

with neurofibromatosis, followed by the amplification of the same polymorphic markers from the offspring from the blood sample, followed by the comparison of the markers from that of the offspring to those of the individual.

Claims 1-16 of the '477 patent are a narrower species drawn to a particular type of condition, while the claims of the instant application is drawn to a genus of tumor suppressor gene disease. Hence, claims of the '477 patent are narrower species of the genus claims of the instant application.

In the instant situation, the narrower species claims necessarily renders the genus claims of the instant application obvious in an "anticipatory" way.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is

on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m (M-W and F). The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Young J. Kim
Primary Examiner
Art Unit 1637
4/11/2007

YOUNG J. KIM
PRIMARY EXAMINER

YJK